Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

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Abstract: BACKGROUND: Radiotherapy is the standard care in elderly patients with malignant astrocytoma and the role of primary chemotherapy is poorly defined. We did a randomised trial to compare the efficacy and safety of dose-dense temozolomide alone versus radiotherapy alone in elderly patients with anaplastic astrocytoma or glioblastoma. METHODS: Between May 15, 2005, and Nov 2, 2009, we enrolled patients with confirmed anaplastic astrocytoma or glioblastoma, age older than 65 years, and a Karnofsky performance score of 60 or higher. Patients were randomly assigned 100 mg/m(2) temozolomide, given on days 1-7 of 1 week on, 1 week off cycles, or radiotherapy of 60 · 0 Gy, administered over 6-7 weeks in 30 fractions of 1 · 8-2 · 0 Gy. The primary endpoint was overall survival. We assessed non-inferiority with a 25% margin, analysed for all patients who received at least one dose of assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01502241. FINDINGS: Of 584 patients screened, we enrolled 412. 373 patients (195 randomly allocated to the temozolomide group and 178 to the radiotherapy group) received at least one dose of treatment and were included in efficacy analyses. Median overall survival was 8 · 6 months (95% CI 7 · 3-10 · 2) in the temozolomide group versus 9 · 6 months (8 · 2-10 · 8) in the radiotherapy group (hazard ratio [HR] 1 · 09, 95% CI 0 · 84-1 · 42, p(non-inferiority)=0 · 033). Median event-free survival (EFS) did not differ significantly between the temozolomide and radiotherapy groups (3 · 3 months [95% CI 3 · 2-4 · 1] vs 4 · 7 [4 · 2-5 · 2]; HR 1 · 15, 95% CI 0 · 92-1 · 43, p(non-inferiority)=0 · 043). Tumour MGMT promoter methylation was seen in 73 (35%) of 209 patients tested. MGMT promoter methylation was associated with longer overall survival than was unmethylated status (11 · 9 months [95% CI 9 · 0 to not reached] vs 8 · 2 months [7 · 0-10 · 0]; HR 0 · 62, 95% CI 0 · 42-0 · 91, p=0 · 014). EFS was longer in patients with MGMT promoter methylation who received temozolomide than in those who underwent radiotherapy (8 · 4 months [95e% CI 5 · 5-11 · 7] vs 4 · 6 [4 · 2-5 · 0]), whereas the opposite was true for patients with no methylation of the MGMT promoter (3 · 3 months [3 · 0-3 · 5] vs 4 · 6 months [3 · 7-6 · 3]). The most frequent grade 3-4 intervention-related adverse events were neutropenia (16 patients in the temozolomide group vs two in the radiotherapy group), lymphocytopenia (46 vs one), thrombocytopenia (14 vs four), raised liver-enzyme concentrations (30 vs 16), infections (35 vs 23), and thromboembolic events (24 vs eight). INTERPRETATION: Temozolomide alone is non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma. MGMT promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making. FUNDING: Merck Sharp Dohme.

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*The NOA-08 randomized phase III trial of c*hemotherapy *versus* radiotherapy for malignant astrocytoma in the elderly

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ABSTRACT

Background

While radiotherapy (RT) is standard-of-care in elderly patients with malignant astrocytoma, the role of primary chemotherapy is poorly defined. The NOA-08 trial compared efficacy and safety of RT to temozolomide (TMZ) in patients with anaplastic astrocytoma (AA) or glioblastoma (GB).

Methods

Patients (N=412; 39 AA, 373 GB) > 65 years with a Karnofsky performance score $\geq$ 60 were randomized in electronically generated blocks of variable length without stratification to receive standard RT to 60 Gy in 30 x 2 Gy fractions or TMZ in a one week on/one week off schedule. The primary endpoint was overall survival (OS). This trial (German Cancer Trials Registry ID 386 and NCT01502241) sought to demonstrate non-inferiority with a 25% margin of dose-dense TMZ compared with RT in the intention-to-treat population. The trial finished enrolment Nov 2 2009. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3·0.

Findings

Patient characteristics in the intention-to-treat population [N=373 (178 patients RT, 195 patients TMZ)] were balanced. Median OS [8·6 [7·3-10·2] months versus 9·6 [8·2-10·8] months; hazard ratio (HR)=1·09 (95% CI: 0·84-1·42)] of TMZ *versus* RT did not differ between both arms. Non-inferiority of TMZ compared with RT was significant (p=0·033). Also median event-free survival (EFS) [3·3 [3·2-4·1] months versus 4·7 [4·2-5·2] months did not differ with a HR=1·15 (0·92-1·43)] indicating non-inferiority (p=0·043). DNA repair protein O^6-*methylguanine DNA-methyltransferase* (*MGMT*) promoter methylation in tumor tissue (73/209 patients, 34·9%) tested was associated with prolonged OS [11·9 [9-not reached] versus 8·2 [7-10] months; HR=0·67 (0·38-1·29), p=0·0137]. Patients with *MGMT* promoter methylation had longer EFS when treated with TMZ (8·4 months [5·5-11·7] *versus* RT (4·6 [4·2-5] months) whereas patients without *MGMT* promoter methylation had longer EFS when

treated with RT (4·6 [3·7-6·3] *versus* 3·3 [3-3·5] months). The most common intervention-related adverse events in each group were leukocytopenia, lymphocytopenia and thrombocytopenia (grade 3/4 according to CTCAE: 12/4, 24/2, and 12/2 in the TMZ and 2, 1, and 4 in the RT arm), liver enzyme elevation (grade 3/4: 26/4 in the TMZ and 12/4 in the RT arm), infections (grade3/4: 26/9 in the TMZ and 15/8 in the RT arm), and thromboembolic events (grade 3/4: 18/6 in the TMZ and 1/4 in the RT arm).

Interpretation

NOA-08 demonstrates the non-inferiority of TMZ compared with RT in the treatment of elderly patients with malignant astrocytoma. To improve EFS, *MGMT* promoter methylation is a strong predictive biomarker for the choice between RT and TMZ.

Funding

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Keywords: glioma, radiotherapy, temozolomide, MGMT

INTRODUCTION

Gliomas account for half of all intrinsic brain tumours and glioblastoma (GB) of World Health Organization (WHO) grade IV, the most malignant variant of glioma, accounts for half of all gliomas. On a population level, median survival with GB may still be below 6 months and age is the most important therapy-independent prognostic factor (www.cbtrus.org).[1] In a few years more than half of the patients with GB will be older than 65 years of age and thus be classified as elderly.[2] In the elderly, anaplastic astrocytoma (AA) (WHO grade III), a less common and malignant type of glioma with an overall better prognosis, shares molecular features and poor outcome with GB.[3,4]

The current standard of care in elderly patients with GB or AA is resection or biopsy followed by involved-field radiotherapy (RT).[5] The classical treatment schedule of RT consists of 60 Gy in 30 fractions of 2 Gy although a hypofractionated schedule, e.g., 15 x 2·66 Gy[7] is used in some centres. Concomitant and adjuvant radiochemotherapy with the alkylating agent temozolomide (TMZ) has become the standard of care in the younger population of GB patients.[7] However, the benefit from TMZ is largely restricted to patients with tumours exhibiting promoter methylation of the *O^6-methylguanine-DNA methyltransferase* (*MGMT*) gene, which encodes a DNA repair protein associated with alkylator resistance.[8,9] However, the benefit derived from the addition of chemotherapy decreases with age[10] and age *per se* is considered a risk factor for cognitive side effects from cranial irradiation.[2] Moreover, the tolerability of combined modality treatment of RT plus TMZ in the elderly appears to be reduced.[11] Accordingly, TMZ chemotherapy alone has been explored and found to be feasible in GB of the elderly.[12,13] Finally, we had reported encouraging progression-free survival rates at six months in patients with recurrent glioblastoma treated with a one week on one week off regimen.[14] These promising studies encouraged the German Neurooncology Working Group (NOA) in 2005 to conduct a randomized phase III trial (NOA-08) to demonstrate that dose-dense TMZ alone was not inferior to RT alone in the

management of newly diagnosed GB or AA in the elderly (> 65 years) and to evaluate the role of *MGMT* promoter methylation in this patient group.

PATIENTS AND METHODS

Patients

Patients with *de novo* histologically confirmed AA or GB and > 65 years of age, Karnofsky performance score (KPS) ≥ 60, no prior systemic chemotherapy or RT to the brain, and adequate bone marrow reserve, liver, and renal function were eligible. Inclusion into the trial was based on local diagnosis. Histologic diagnoses were confirmed centrally at the Brain Tumour Reference Centre, German Society for Neuropathology and Neuroanatomy, in Düsseldorf at study entry, according to the WHO classifications 2000[15] and 2007[16]. Failure to confirm AA or GB would have resulted in exclusion from the intention-to-treat-population (ITT). Of note, there was no change in the diagnostic criteria for AA or GB between the two versions of the WHO classification.

Trial Design and Treatment

NOA-08 (German Cancer Trials Registry ID 386 and NCT01502241) was approved by the ethics committees (EC) of all 23 participating sites. The study was conducted from May 15 2005 through November 2 2010, with the last patient randomized on Nov 2 2009. The principal screening population consisted of patients who fulfilled the inclusion criteria histology, age and KPS. All study patients provided written informed consent. Patients were centrally randomized 1:1 to receive RT or TMZ in a one week on/one week off schedule (see Supplementary Information) (Fig. 1). At progression, treatment with TMZ in the RT arm and with RT in the TMZ arm was suggested in the protocol.

If toxicity in the TMZ arm resulted in delays longer than 4 weeks prior to six months of treatment, TMZ was stopped and RT was performed. Treatment was stopped at disease progression or for unacceptable toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3·0.

Randomization and Masking

Sequence generation: Participant allocation was done according to an electronically generated randomization list in blocks of variable length without stratification. The sequence was generated prior to study start at the independent Contract Research Organization (CRO), alcedis (Gießen, Germany).

Allocation concealment: Enrolment was done at the study site by an investigator. Assignment was initiated by FAX transmission from the study site to the CRO for single patients fulfilling the eligibility criteria. A responsible project manager at the CRO performed the randomization process and reported the assignment to the trial group via FAX transmission to the study site.

Blinding and masking: Due to the procedures necessary for RT or TMZ treatment, blinding of investigators or participants was impossible. Similar the data had to be analysed with knowledge of the group assignment. Biases were prevented by strict adherence to an analysis plan that was written by the statistician (C.M) and approved by the lead investigators (W.W. and M.W.) prior to any analysis on the data.

Evaluations

Baseline examinations included physical examination, MRI, full blood cell counts, blood chemistry, Mini-Mental State Examination (MMSE), and quality-of-life questionnaire (QLQ) assessment with European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30 and BN-20. Patients received monthly clinical evaluation during therapies and a more comprehensive evaluation, which included MRI, MMSE, and QLQ 4 weeks after completing RT or 3 months after initiation of TMZ and every 3 months thereafter. In the RT arm full blood cell counts and blood chemistry were done at 4 weeks after starting RT. In the TMZ arm, full blood counts were done weekly and blood chemistry was done every 4 weeks during treatment. Toxicity was assessed biweekly. Tumour response or progression were defined according to Macdonald criteria[17] (see Supplementary Information). Importantly, an apparent increase in tumor volume or contrast-enhancement in the radiation field in the first scan post RT was not deemed a progression but resulted in re-MRI 4-6 weeks later.

Molecular Methods

The *MGMT* promoter methylation status (see Supplementary Methods) was determined by two distinct methylation-specific PCR (MSP) assays.[18,19] Real-time PCR-based quantitative testing on 182 samples revealing 152 conclusive results was done at MDX Health.[19] These same samples plus 70 samples from stereotactic biopsies with another 57 conclusive results were evaluated by conventional MSP at the German Brain Tumor Reference Center.[18] Where discrepancies were detected (in 4 samples; twice in each direction), the results from MDX Health were used.

Statistical analysis

The primary endpoint was overall survival (OS), measured in days from surgery to death. Secondary efficacy end points included EFS, best response, health-related quality of life (HRQOL) and safety. Event-free survival (EFS) was defined as time from surgery to first progression for patients with progression respectively to death for patients without progression. Patients without progression or death were censored at the day of the last contact. Univariate descriptive analysis of OS and EFS used Kaplan-Meier estimates[20] and a Cox proportional hazard model for estimating Hazard Ratios (HR) with two-sided 95%-confidence intervals (CI) and median OS and EFS with two-sided 95%-confidence intervals. The non-inferiority of TMZ compared to RT concerning OS and EFS was evaluated using a one-sided Log Rank test as described[21,22] for a tolerance level of -25% difference (radiotherapy group – TMZ group) in median OS respectively EFS. Only OS was analyzed for confirmatory analysis and – regarding the non-inferiority hypotheses based on Hazard ratio, decided for a one-sided significance level of 0·05.

The best responses[17] in both arms were compared using Wilcoxon test. Multivariate analyses and HRQOL assessment[23,24] is detailed in Supplementary Methods. All analyses of the primary and secondary efficacy endpoints were based on the intention-to-treat population, which included all randomized patients except patients who withdrew their

consent for data analysis or patients who did not receive any dose of trial medication after randomization. The per-protocol analysis of the primary endpoint included only patients without major protocol violations; these were unconfirmed histological confirmation of diagnosis (n=2) and age ≤ 65 years (n=9). The safety analyses concentrates on the documentation of adverse events (details in Supplementary Methods).

The sample size of the trial was based on the primary endpoint and the non-inferiority hypothesis with an equivalence/non-inferiority limit of - 53 days or -25% of an assumed median OS of 7 months a one-sided significance level of 5%, a recruitment duration of 48 months and a drop-out of 11%.

Then, 412 subjects were found to be sufficient to achieve at least 80% power using the test procedure for testing the non-inferiority of TMZ for OS.[21,22] Analyses were performed with Statistical Analysing Program SAS 9·1·3 (SAS Institute, Cary, NC). Alpha error was set to 5% for all tests in this study. The data were documented during the study into the study documentation RDE system of Alcedis (Gießen, Germany). Alcedis monitored the data quality.

This trial is registered as an International Standard Randomised Controlled Trial at the German Cancer Trials Registry (ID 386, quality level A) and with ClinicalTrials.gov (NCT01502241).

Role of the funding sources

The funding source, former Schering Plough, now Merck, Sharp & Dohme, had no role in the study design, collection, analysis, or interpretation of the data or in writing the study report or manuscript. Access to the raw data was limited to W.W., C.M., J.F., G.R. and M.W. The corresponding author had full access to all of the data and the final responsibility to submit the publication.

RESULTS

Patient characteristics

The ITT population consisted of 373 elderly patients with centrally reviewed AA (11%) or GB (89%) who were randomized between May 15 2005 and November 2 2009 and received at least one dose of dose-dense TMZ or one fraction of RT. The per-protocol population consisted of 362 patients. The mean age of the ITT patients was 71 (RT arm) and 72 (TMZ arm) years, and risk factors were well balanced. Of note, there was a tendency to use steroids when RT was administered (Table 1). A total of 149 patients completed RT, and 126 patients in the TMZ group completed at least 4 cycles (8 weeks) of chemotherapy. Patients in both arms had similar frequencies of salvage therapies (74 patients (70%) in the RT arm and 88 patients (62%) in the TMZ arm), which mainly consisted of TMZ in the RT arm and *vice versa* (Supplementary Table 1). The likelihood of receiving salvage therapy did not differ between patients with *MGMT* promoter methylated or unmethylated tumors (data not shown).

Tolerability and toxicity

In general, most patients tolerated both treatments well. There were no CTCAE grade 5 toxicities in this study. CTCAE grade 2 - 4 toxicities were more frequent in the TMZ arm in all categories except for cutaneous AE (Table 2). The main reasons for discontinuation of RT were disease progression (n=10) and prolonged infection (n=8). The median number of TMZ cycles in arm B was 5 (range: 0-20). Discontinuations occurred due to progression (n=141) or toxicity (n=28).

Clinical Efficacy

At a minimal follow-up of 12 months (median 25·2 months [20.0-not reached (NR)]) after the last patients had been randomized, 228 deaths have been observed in the first year (RT: 107, TMZ: 121). The estimation for the 1-year-OS rate was 37·4% (95%-CI: 30·2% – 44·7%)

in the RT arm with a median OS of 9·6 months [95%-CI: 8·2-10·8]. The TMZ group had an estimated 1-year OS of 34.4% (95%-CI: 27·6% - 41·4%) and a median survival of 8·6 months [95%-CI: 7·3-10·2]. The non-inferiority of TMZ in comparison to RT for a tolerance level of 25% was statistically confirmed (Wellek test procedure, tolerance-level 25%: p=0·033)[21,22] with a HR of 1·1 (95%-CI: 0·84 – 1·42) (Table 3 and Fig. 2a). The non-inferiority of TMZ was also confirmed in the analysis of the per-protocol population (Wellek test procedure, tolerance level 25%: p=0·028).

Three-hundred-twenty-five patients experienced an event (progression or death) within in the first 12 months after surgery. There was no evidence for pseudoprogressions. The estimate for the 1-year-EFS rate was 9.3% (95%-CI: 5·5% – 14·3%) in the RT arm with a median EFS of 4·7 months [95%-CI: 4·2-5·2] and 156 events. The TMZ group had an estimated 1-year EFS of 12.0% (95%-CI: 7·8% - 17·1%) and a median EFS of 3·3 months [95%-CI: 3·2-4·1] and 169 events, which comprised toxicities and deaths without documented progression (Wellek test procedure, tolerance-level 25%: p=0·043)[20, 21] with a HR of 1·15 (95%-CI: 0·92 – 1·43) (Table 3 and Fig. 2b). The non-inferiority of TMZ for EFS was also confirmed in the analysis of the per-protocol population (Wellek test procedure, tolerance level 25%: p=0·041)[21, 22].

In the RT arm 106 patients experienced a progression. Seventy-four patients (69·8%) received salvage therapy, whereas 88 of 141 patients (62·4%) with progression received salvage therapy in the TMZ arm (p=0·227). There was a higher likelihood of second surgery in the TMZ arm [p=0·102; relative risk 1·6 (95% CI: 0·9 – 2·9)]. Otherwise, the patients in both arms had a similar frequency of salvage therapy, mainly TMZ in the RT arm, and *vice versa* (Supplementary Table 1).

Prognostic and Predictive Factors

MGMT promoter methylation was analysed for a subgroup of 209 patients (Table 1). This subgroup was comparable to the group of 165 patients without *MGMT* promoter methylation status concerning the distribution of type of primary surgery, histology, age and therapy

group. *MGMT* promoter methylation was detected in 73 of 209 evaluable patients (35%) (Table 1). This value was also detected in the subgroup of stereotactic biopsies with 20 of 59 tested samples showing a *MGMT* promoter methylation (33·8%). The patients tested are representative for the ITT population in all relevant aspects and stereotactic biopsies resembled overall testing results (data not shown). Extent of resection (complete *versus* incomplete or biopsy; incomplete *versus* biopsy), and *MGMT* promoter methylation in tumor tissue, but not age in years neither as a continuous variable or dichotomized at age 70, or histology (AA *versus* GB) was found to be an independent prognostic factor for OS in the multivariate Cox analysis. An interaction was found between *MGMT* promoter methylation (methylated *versus* unmethylated) and therapy (Table 4a, Fig. 2c). These results were found also for EFS (Table 4b, Fig. 2d).

Importantly, *MGMT* promoter methylation was associated with improved EFS only in the TMZ arm, but not in the RT arm (Fig. 2e,f, Table 4, Supplementary Table 2). In the TMZ arm, median EFS for patients with a methylated *MGMT* promoter was 8·5 months (95%-CI 5·6-11·9 days) compared with 3 months (95%-CI 2·6-3·3 days) for patients with an unmethylated *MGMT* promoter (Fig. 2f and Supplementary Table 2b). In contrast, *MGMT* promoter methylation did not influence EFS in the RT arm. However, in patients with a methylated *MGMT* promoter EFS (and with a trend for OS) was worse with RT than with TMZ while in patients with an unmethylated *MGMT* promoter EFS (and with a trend for OS) was superior with RT than with TMZ (Fig. 2e,f and Supplementary Table 2b).

Quality-of-Life Assessments

HRQOL was comparable in both groups and available from 82% of all patients. No clinically meaningful or statistically remarkable difference between the two groups over time in any of the scales or cohorts were observed in any of the three cohorts, except more discomfort from communication deficits in the RT arm for patients who died between 6 and 12 months (p=0·002). Supplementary Figure 1 shows the trajectories of the HRQOL mean scores.

DISCUSSION

NOA-08 broadens the spectrum of primary treatment of elderly patients with malignant gliomas by demonstrating the non-inferiority of primary treatment of elderly patients with malignant gliomas with TMZ alone. It implements *MGMT* promoter methylation as a relevant biomarker to decide, when patients may be undertreated with primary RT alone.

The current standard of care for the increasing population of elderly patients with GB or AA is surgery or biopsy followed by RT.[5] While RT alone is superior to best supportive care in elderly patients with GB and does not reduce QOL[5], age *per se* may be a risk factor for cognitive side effects of cranial irradiation[2], yet solid evidence for such cognitive side effects only exists for younger patients with irradiated low-grade tumors.[25] Whether the addition of chemotherapy to RT[7] improves outcome in the elderly, too, is currently explored. Many elderly patients do not even receive chemotherapy at recurrence.[26] To challenge this current practice, new trial data are needed. In a recent ANOCEF trial, elderly patients > 70 years even with a low KPS < 70 seemed to benefit from TMZ alone when compared to historical controls.[27] The NOA-08 trial for the first time demonstrates that dose-dense TMZ followed by RT as salvage is an alternative option in this patient population that is not inferior to RT alone followed by TMZ as salvage therapy. Given the limited life expectancy, dose-dense TMZ may be particularly suited for patients who may not have easy access to a radiation oncology facility and who prefer an oral medication administered and monitored close to home. However, a decline in cognitive functioning by RT should not be used for decision-making since neither the NOA-08 data nor a previously published trial[5] support a relevance of this presumed unwanted effect (Table 1 and Supplementary Fig. 1), although formal neurocognitive testing was not performed as a meaningful differentiation between the in part rapid disease progression (Table 3, supplementary Table 2b) and an evolving neurocognitive deficit was regarded impossible.

More importantly, the major novelty reported here is the strong predictive power of the *MGMT* status for the benefit to be expected from either treatment modality for EFS and as a yet non-significant trend for OS: *MGMT* promoter methylated tumours respond better to TMZ

whereas unmethylated tumours respond better to RT (Fig. 2e,f, Table 4a,b). The data do not indicate that the non-significant effect for OS is due to resolving pseudoprogressions in the RT arm for methylated patients, but that these patients do better respond to the salvage TMZ treatment (Fig. 2e). The concept of pseudoprogression, although not the explicit terminology was well known at all study sites and regularly ruled out by short interval re-scanning with MRI. Such stratification by a single biomarker has not been established in neurooncology despite supportive landmark data[7,8] and is rare in general oncology, too. Accordingly, despite the acknowledged challenges associated with *MGMT* promoter methylation testing[9], our data confirm the hypothesis generated by the recent cohort analysis of the German Glioma Network[28], and in conjunction justify or even call for the routine testing of the *MGMT* promoter status in elderly patients with GB or AA, (i) to improve outcome, (ii) to prevent unnecessary toxicity and (iii) to save cost.

NOA-08 has its limitations, not only because of the inherent weaknesses of a non-inferiority design, the selection of a generous tolerance level, a one-sided test procedure and possible non-proportional hazards for EFS. Only 56% of the tissues were available and informative for *MGMT* testing. The limited number of informative results is mainly due to the high percentage of stereotactic biopsies (Table 1), which may not qualify for MGMT testing due to the limited amount of tumour DNA that can be extracted from these small tissue specimens. Still, both the results from the testing of stereotactic biopsies resembled overall testing results and the patients tested are representative for the ITT population in all relevant aspects. While TMZ exhibited haematological toxicity, liver enzyme elevations, asthenia/fatigue and gastrointestinal side effects in a relevant number of patients, more severe grade 4 toxicity was rare (Table 2). This toxicity may well be due to the intensified dosing schedule used in this trial and particularly careful to evaluate in this elderly patient population, where also grade 2 toxicities may impact quality of life. In a recent trial in younger patients with GB, dose intensification in the adjuvant setting of primary combined modality treatment was not associated with increased OS, neither in patients with

methylated nor with unmethylated *MGMT* promoter status.[29] Thus, it may well be that TMZ alone can be given in a conventional schedule in elderly patients with *MGMT* promoter methylated malignant glioma with comparable efficacy as demonstrated in this trial but reduced toxicity. However, at the time this trial was designed and conducted, there were no data that compared different TMZ schedules, but only data indicative of a superior efficacy of the dose-dense TMZ schedule[14], which also led to the design of the glioblastoma trial 0525 by the Radiation Therapy Oncology Group, which is reported to be negative.[29] Similar, information on the potential non-inferiority of shorter courses of RT were only evolving, when NOA-08 already had been designed.[6,30]

The age cut-off of 65 years to define elderly patients remains a controversial issue in neurooncology and even arbitrary in some patients.[2] While it may shift towards 70 in the field of GB, it may shift to 60 in primary brain lymphoma where more aggressive treatments are explored. Other factors, such as neurological function or comorbidities are relevant, while in a generally well trial cohort such as the NOA-08 trial population, age alone is not prognostic any more (Table 4).

We propose that future research efforts should explore the biological basis underlying the poorer outcome associated with gliomas in the elderly and should step-wise replace age *per se* as a basis for clinical decision making. In this regard, the identification of *IDH1* mutations as a positive prognostic marker restricted to gliomas of younger patients was a first important step.[4] AA in the elderly and primary GB both typically lack of *IDH1* mutations and show a similar, unfavourable outcome[3,4], justifying the inclusion of AA patients in this trial and the focus on *MGMT* but not *IDH* testing. In the limited number of non-GB patients included (Table 1), however, we find that AA patients do better with both treatments (HR 0·7, Table 4), albeit worse than younger patients with AA in previous trials.[31,32] In that respect, the IDH-associated glioma-CpG island methylator phenotype-related profiles[32] may dilute the predictive properties of *MGMT* promoter methylation demonstrated in the NOA-08 trial, thus providing a possible explanation why MGMT lacks predictive properties in anaplastic glioma in younger patients.[31]

In summary, NOA-08 demonstrated that TMZ chemotherapy alone is not inferior to RT alone in elderly patients with newly diagnosed GB or AA. This practice-changing observation will be confirmed in the independent Nordic trial that also reported a similar efficacy of RT alone and TMZ, albeit in a different regimen of 5 days TMZ out of 28 days, and in patients with GB aged 61 or more.[30] More importantly, NOA-08 defines *MGMT* promoter methylation as a strong predictive biomarker that should help to guide clinicians to select among these two therapeutic options (Fig. 2 e,f and Supplementary Table 2). As a complementary approach and a next step of standardizing treatment of elderly patients with gliomas, the joint study of NCIC (CE·6) and EORTC (26062/22061) explores the efficacy of RT *versus* RT *plus* TMZ in elderly patients with GB. NOA-08 will certainly provoke a discussion on the standard-of-care arm, RT, in the methylated patients, especially since these patients do not shown a superior benefit from salvage TMZ compared to the unmethylated patients (Fig. 2e). Data from the NCIC/EORTC study may further validate the role of *MGMT* as a predictive biomarker in this patient population. It may confirm that TMZ produces no benefit in patients with unmethylated tumours, but, in case of a positive outcome, will provoke the question whether TMZ alone with deferred RT may be a sufficient treatment in patients with *MGMT* promoter methylated tumours.

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The study has been awarded the quality label A by the German Cancer Society.

Alcedis (Giessen, Germany) served as CRO for monitoring and data collection.

The first round of *MGMT* testings reported in this study was done as a free scientific service by MDx Health (Liège, Belgium).

A preplanned event-driven analysis of the primary endpoint was presented at the ASCO Meeting 2010 (Wick W, Engel C, Combs SE et al. J Clin Oncol 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 2010;Vol 28:LBA 2001 (No 18 suppl (June 20 Supplement)) (for details see Supplementary Note).

CONFLICT OF INTERESTW.W., J.P.S, G.R. AND M.W. report on having received consulting and lecture fees from MSD. W.W. and M.W. have received research support from MSD.

M.P., C.M., J.F., G.T., M.S., G.N., K.P., M.S., S.E.C., J.V., C.B., J.M., R.K., and R.M.-S. declare no conflicts of interest.

CONTRIBUTORS

The concept of the trial was developed by M.W. and W.W. in collaboration with the German Neurooncology Working Group (NOA) in the German Cancer Society.
All data were collected by Alcedis and reviewed by W.W.
The statistical analyses were performed by C.M., a statistician at the Institute of Medical Biometry in Tübingen assisted by Rainer Stolper.
Histological specimens were reviewed centrally at the Brain Tumor Reference Centre of the German Society for Neuropathology and Neuroanatomy at the University of Düsseldorf Medical Centre by G.R. and J.F.
Analysis of the MGMT promoter methylation status was performed by MDx Health Care and by J.F. and G.R.
The article was written by W.W and M.W. with support from M.P., C.M., J.F., G.T., M.S., G.N., K.P., J.P.S., M.S., S.E.C., J.V., C.B., J.M., R.K., R.M.-S., G.R..
W.W., M.P., C.M., J.F., G.T., M.S., G.N., K.P., J.P.S., M.S., S.E.C., J.V., C.B., J.M., R.K., R.M.-S., G.R. and M.W. reviewed and approved the manuscript.

FIGURE LEGENDS

Figure 1. Trial design and CONSORT flow chart. Patients were randomized 1:1 to receive RT or TMZ chemotherapy in an one week on/ one week off schedule. Patient numbers represent the intention-to-treat population. At progression, patients treated initially with RT were commonly treated with TMZ. Patients who progressed on or after TMZ were often treated with RT (Abbreviations: intention-to-treat population, ITT; radiotherapy, RT; temozolomide, TMZ).

Figure 2. Kaplan-Meier survival estimates. Data of OS (panel a) or EFS (panel b) were analyzed by treatment arm and tested for non-inferiority or by *MGMT* promoter methylation status (*MGMT* promoter methylated (*MGMT*+) or unmethylated (*MGMT*-), panels c and d) and tested for difference. Of note, Fig. 2b is presenting non-proportional curves, which are deemed unproblematic in the context of non-inferiority. Data of OS (panel e) or EFS (panel f) of the TMZ- or RT-treated patients were also analyzed by *MGMT* promoter methylation status (*MGMT* promoter methylated (*MGMT*+) or unmethylated (*MGMT*-) and tested for difference.

Figure 1

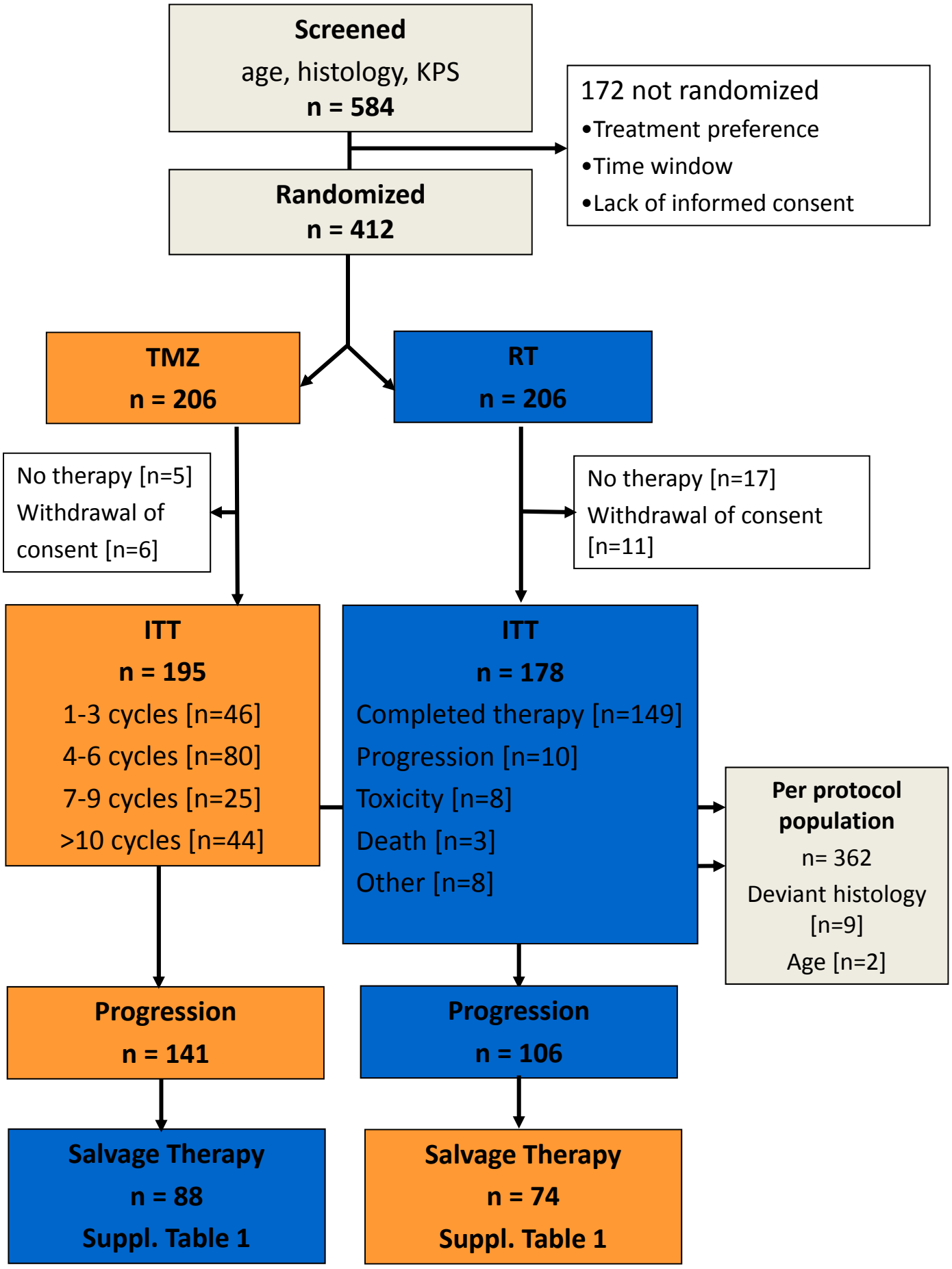
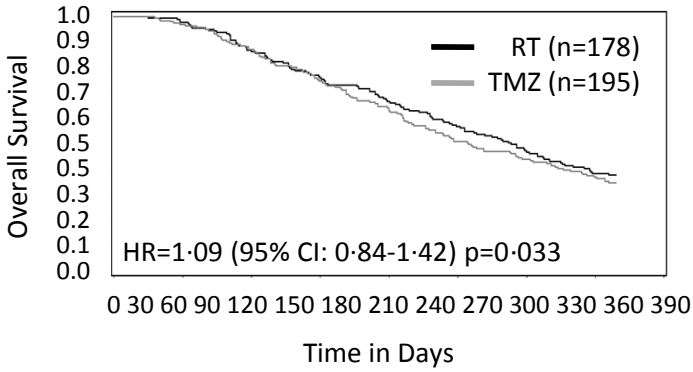

Screened
age, histology, KPS
n = 584
172 not randomized
•Treatment preference
•Time window
•Lack of informed consent
Randomized
n = 412
TMZ
n = 206
RT
n = 206
No therapy [n=5]
Withdrawal of consent [n=6]
No therapy [n=17]
Withdrawal of consent [n=11]
ITT
n = 195
1-3 cycles [n=46]
4-6 cycles [n=80]
7-9 cycles [n=25]
>10 cycles [n=44]
ITT
n = 178
Completed therapy [n=149]
Progression [n=10]
Toxicity [n=8]
Death [n=3]
Other [n=8]
Per protocol population
n= 362
Deviant histology [n=9]
Age [n=2]
Progression
n = 141
Progression
n = 106
Salvage Therapy
n = 88
Suppl. Table 1
Salvage Therapy
n = 74
Suppl. Table 1

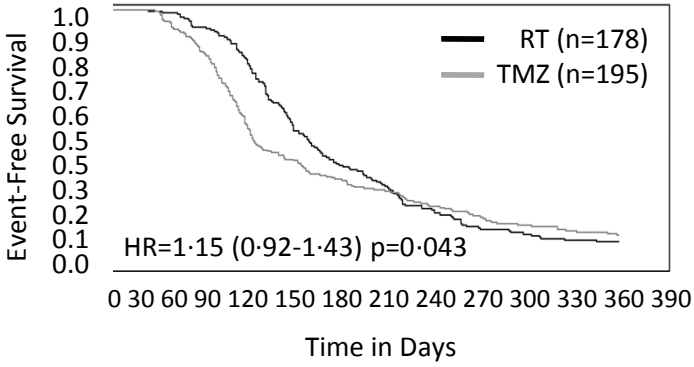
Figure 2

a



Time/ Pts at risk	30	60	90	120	150	180	210	240	270	300	330	360	390
RT 178	176	168	154	142	130	123	110	100	90	79	67	59	53
TMZ 195	194	187	170	152	140	122	111	96	85	78	69	60	52

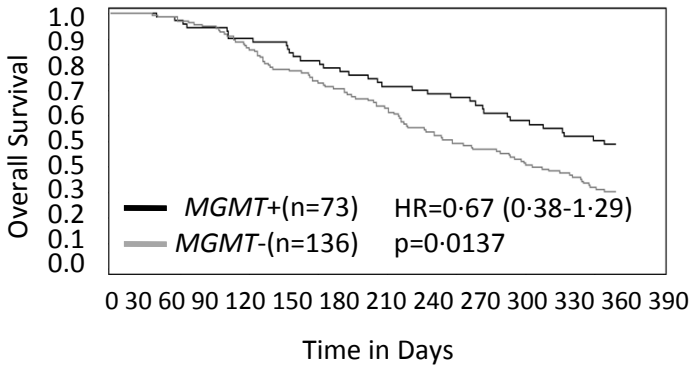
b



Time/ Pts at risk	30	60	90	120	150	180	210	240	270	300	330	360	390
RT 178	176	164	145	108	75	62	41	34	24	21	16	15	10
TMZ 195	194	168	119	83	68	58	50	42	33	29	25	23	22

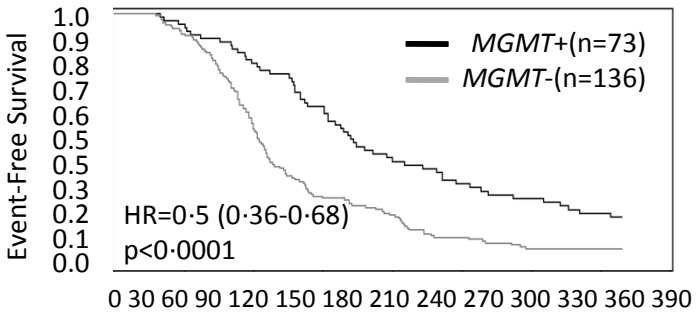
Figure 2

c



Time/ Pts at risk	30	60	90	120	150	180	210	240	270	300	330	360	390
MGMT+ 73	72	68	63	62	57	52	49	46	40	38	34	32	31
MGMT- 136	135	129	118	102	95	87	76	66	61	53	47	37	36

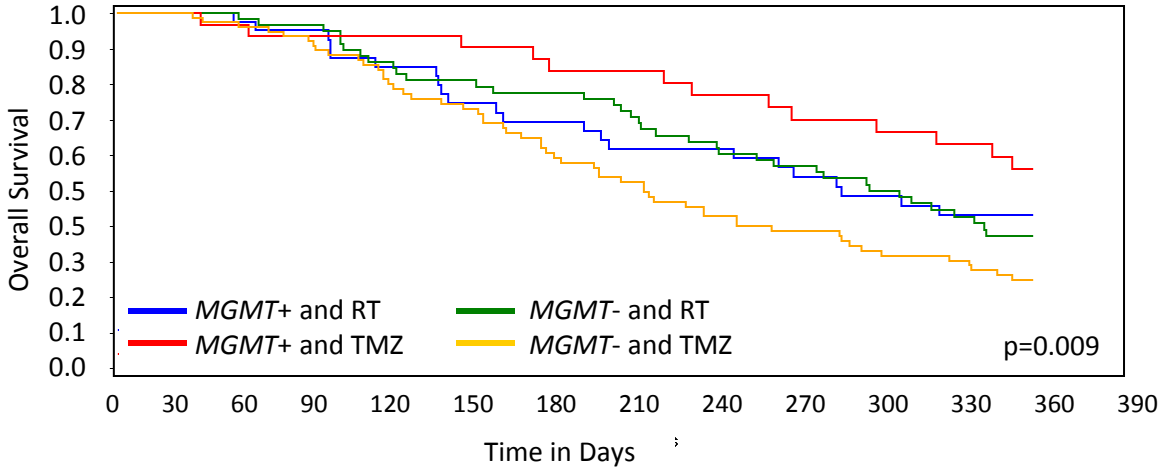
d



Time/ Pts at risk	30	60	90	120	150	180	210	240	270	300	330	360	390
MGMT+ 73	72	66	59	53	44	31	27	23	19	18	15	13	12
MGMT- 136	135	120	88	52	36	32	21	15	12	9	8	7	0

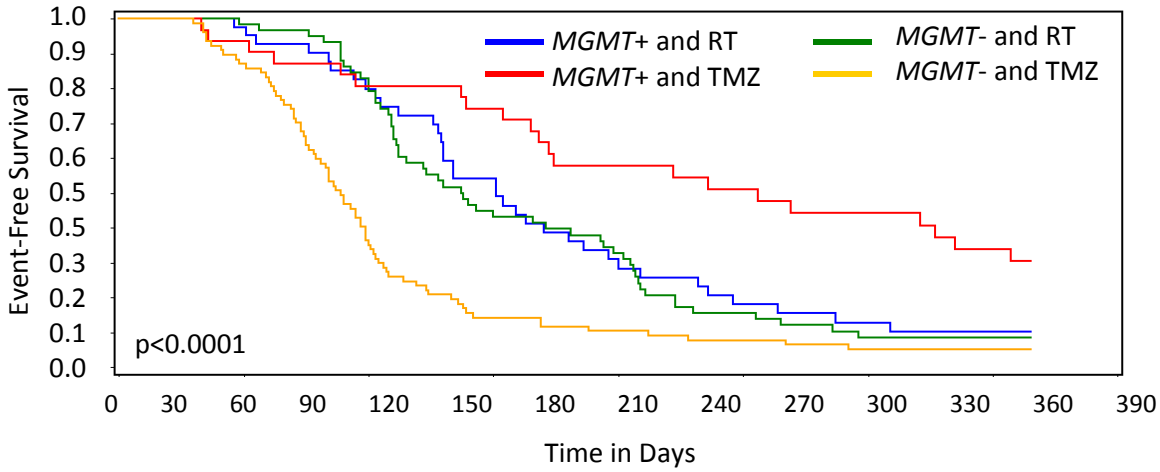
Figure 2

e



Time / Pts at risk		30	60	90	120	150	180	210	240	270	300	330	360	390
RT	MGMT+ 42	41	39	34	33	29	27	24	24	20	18	16	16	15
	MGMT- 59	59	56	52	47	45	45	39	35	33	29	24	19	18
TMZ	MGMT+ 31	31	29	29	29	28	25	25	22	20	20	18	16	15
	MGMT- 77	76	73	66	55	50	42	37	31	28	24	23	18	17

f



Time / Pts at risk		30	60	90	120	150	180	210	240	270	300	330	360	390
RT	MGMT+ 42	41	38	33	28	21	14	10	8	6	5	4	1	0
	MGMT- 59	59	56	50	34	25	23	13	9	7	5	4	1	0
TMZ	MGMT+ 31	30	28	26	25	23	17	17	15	13	13	11	9	8
	MGMT- 77	76	63	37	18	11	9	8	6	5	4	4	1	0

TABLES

Table 1. Baseline Patient Characteristics

	TMZ n = 195	RT n = 178
Median age (range), years	72 (66-84)	71 (66-82)
Sex (female/male), n	107/88	90/88
Central histopathology, n (%)		
AA	17 (9)	23 (13)
GB	178 (91)	153 (86)
Not confirmed	0	2 (1)
Median KPS (range) [%]	80 (60-100)	80 (60-100)
Prior to treatment	70 (20-100)	80 (50-100)
After primary treatment*	70 (0-100)	70 (20-100)
Median Mini-Mental State Examination score (out of 30) (range)	27 (9-30)	27 (13-30)
Prior to treatment	28·5 (17-30)	28 (12-30)
After primary treatment*	28 (0-30)	27 (11-30)
Resection, n		
Complete	53	51
Partial	61	62
Biopsy	80	65
Missing	1	0
Steroids, n		
None	97	36
At the start of treatment only	8	26
At the start and end of treatment*	27	24
At the end of treatment only*	63	90
No data	0	2
Duration of treatment (range) [days]	77 (1-1137)	43 (1-65)
Median time from surgery to start of study treatment (range) [days]	19 (4-47)	30.5 (11-76)
MGMT promoter, n		
Methylated	31	42
Unmethylated	77	59
Missing/inconclusive	87	77

*Determined at first assessment post RT or the first 3 monthly assessment in the TMZ arm, which are both approximately 3 months after randomization.

Table 2. Toxicity: Distinct events as recorded in the AE documentation. A new AE in the same category was counted here if the grade of the prior AE of the same kind had returned to CTCAE grade ≤ 1

	TMZ n = 195			**RT n = 178**		
CTCAE grade	**2**	**3**	**4**	**2**	**3**	**4**
Haematological toxicity, n						
Neutropenia	56	12	4	0	2	0
Lymphocytopenia	60	44	2	4	1	0
Thrombocytopenia	36	12	2	5	4	0
Liver enzyme elevation, n	42	26	4	13	12	4
Infection, n	54	26	9	40	15	8
Thrombembolic event, n	16	18	6	10	4	4
Asthenia / Fatigue, n	37	21	3	23	14	6
Nausea / Vomiting, n	32	6	0	6	1	0
Weight loss / Inappetence, n	8	2	0	2	0	0
Neurologic symptoms	73	27	9	31	18	7
Seizures	14	15	2	9	7	6
Cutaneous AE (dermatitis, allergic rash, alopecia), n	15	1	0	18	1	0

Table 3. OS and EFS

	TMZ **n = 195** (95%-CI)	**RT** **n = 178** (95%-CI)
Median EFS, HR	1·15 (0·92 – 1·43)	
Median EFS, months	3·3 (3·2 – 4·1)	4·7 (4·2 – 5·2)
EFS rate at 6 months, %	30·1 (23·6 – 36·6)	35.1 (28·0 – 42·3)
EFS rate at 12 months, %	12·0 (7·9 – 17·1)	9.3 (5·5 –14·2)
Median OS, HR	1·09 (0·84 – 1·42)	
Median OS, months	8·6 (7·3 – 10·2)	9·6 (8·2 – 10·8)
OS at 6 months, %	66·7 (60·0 – 73·4)	71·7 (65·0 – 78·4)
OS at 12 months, %	34·4 (27·6 – 41·4)	37·4 (30·1 – 44·7)

Table 4a. Prognostic and predictive factors as determined in a multivariate Cox-regression analysis for the primary endpoint OS (n=208 from 373)*.

	Hazard ratio (95% CI)	P value
Age (years)	1·02 (0·98 – 1·06)	0·285
Resection Complete *versus* incomplete *versus* biopsy	1·84 (1·44 – 2·35)	<0·0001
AA *versus* GB	0·69 (0·38 – 1·22)	0·201
TMZ, *MGMT* methylated	0·69 (0·35 – 1·16)	0·139
RT, *MGMT* methylated and unmethylated	1·0 (Reference)	
TMZ, *MGMT* unmethylated (95%-CI)	1·34 (0·92 – 1·95)	0·129

Table 4b. Prognostic and predictive factors as determined in a multivariate Cox-regression analysis for EFS (n=208 from 373)*.

	Hazard ratio (95% CI)	P value
Age (years)	1·01 (0·98 – 1·04)	0·674
Resection Complete *versus* incomplete *versus* biopsy	1·29 (1·07 – 1·56)	0·008
AA *versus* GB	0·75 (0·45 – 1·24)	0·255
TMZ, *MGMT* methylated	0·53 (0·33 -0·86)	0·01
RT, methylated and unmethylated	1·0 (Reference)	
TMZ, *MGMT* unmethylated	1·95 (1·41 – 2·69)	0·01

* 164 without methylation status, 1 without resection status